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The authors designed a randomized, double-blind, crossover study to assess the efficacy of Sertraline in the treatment of Premenstrual Dysphoric Disorder (PMDD) when given only during the luteal phase of the menstrual cycle. Thirty-one subjects were selected for a seven month study period which included an initial two months of screening, two months of treatment with placebo or Sertraline, a washout month, and two months crossed over to either placebo or Sertraline. Eleven subjects completed the study. Symptoms were monitored with daily reports using the Calendar of Premenstrual Experience (COPE). For each study phase premenstrual COPE scores (seven days prior to menses) were examined using repeated measures analysis of variance, with the within-subject factor, time period, and the between-subject factor, study drug order. COPE scores that document both document both behavioral and physical symptoms were analyzed together and separately using the paired t-test. When comparing COPE results during the treatment periods of the luteal phase, there was significant treatment effect, with higher scores during the placebo cycles compared to the Sertraline treated cycles (P=0.0052 behavioral, P=0.012 physical). This study is the first to demonstrate a significant response to an SSRI when used only during the luteal phase. The authors point out the importance of this finding both in terms of economic cost to patients as well as how it may add to the growing understanding of the etiology of PMDD.

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Introduction

The existence of a "pre menstrual syndrome" has long been debated. A nineteenth century psychiatrist wrote:

> "He [the devil] is in her body, burning it and pinching it. He also gnaws at her heart, and rends her entrails. She is surrounded by flames, and in the midst of the fires of hell, though we see them not. No one may credit it, but her ills are unprecedented, frightful, and eternal. She is damned. Heaven can have no compassion on her."
>
> JED Esquriol
>
> Mental Maladies: A Treatise on Insanity (1845)(1)

More recent reports have struggled with the development of reproducible diagnostic criteria (2,3,4), examined various treatment regimens (5-12), and attempted to derive etiologic theories (2,13,14).

Today, the presence of a well circumscribed syndrome of behavioral, affective, cognitive, and somatic changes after ovulation and prior to menses has been well described (2,15,16). Despite concerns about the potential consequences of describing this syndrome as a psychiatric disorder (17), "Late Luteal Phase Dysphoric Disorder" (LLPDD) was included in the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders, 3rd Edition, Revised (DSM-III-R) as a diagnosis "needing further study" (18). DSM-IV designates the disorder in the same fashion, but has simplified the name to "Premenstrual Dysphoric Disorder"(PMDD)(19).

Estimates of the prevalence of PMDD vary greatly, primarily because most women note some of the symptoms on an intermittent basis. Historical reports from patients are quite unreliable (15) and most recent studies have used various prospective self report scales (5-7). Of 839 women sampled in a 1986 report, two to ten per cent of women were reported to have "severe" symptoms of PMDD that may cause "significant impairment" (3). DSM-IV states that the symptoms "must cause an obvious and marked impairment in the ability to function socially or occupationally in the week prior to menses" and occur "most months for the previous 12 months".

A number of reports have examined the pharmacologic treatment of PMDD. These have employed alprazolam (5), fluoxetine (6,7,9,20-23), Valproate (8), Danazol (10), Nortriptyline (11), bright light (12), buspirone (24), and a Gonadotropin Releasing Hormone (GnRH) agonist (D-Tryp6-Pro9-NEt-GnRH) (25). While Danazol and the GnRH agonist have both shown promise, side effects pose significant problems with both regimens (15). Fluoxetine treatment has clearly been shown to be beneficial, demonstrating statistically significant improvement in the majority of patients studied. These studies have primarily treated the subjects during the entire menstrual cycle. There is one case report of the use of Fluoxetine in a single dose given seven days prior to the onset on menses (9). At the time of the report the subject had been treated for four cycles and reported significant improvement in each. The excessive half life of Fluoxetine combined with the long term cost of the regimen make daily indefinite treatment a potentially limited tool in clinical settings. The present study employed Sertraline, a Selective Serotonin Reuptake Inhibitor (SSRI) with a much briefer half life (24 hours as opposed to 7 days for Fluoxetine). Additionally, patients were treated only during the luteal phase of the cycle, thus lessening cost and long term exposure to psychotropic medication. There has been one recent report of an unpublished study in which Sertraline was shown to be effective in PMDD (26).

Methods:

A randomized, double-blinded, placebo-controlled crossover trial was conducted at the Walter Reed Army Medical Center from October 1994 to July 1995. Thirty one study subjects between the ages of 18 and 45 were selected from approximately 50 responders to advertisements in local military newspapers and posted in gynecology clinics. They were not paid. Potential subjects were screened by telephone using DSM-IV criteria (19) . Those with a history of any mental health treatment in the previous 18 months or who were taking psychotropic medication were excluded. After complete description of the study to the subjects, written informed consent was obtained. This protocol was reviewed and approved by the Human Use Committee/Institutional Review Board at Walter Reed.

This initial group then entered the assessment phase of the study, a two month period of daily symptom reporting utilizing the Calendar of Premenstrual Experiences (COPE) (27), a PMDD assessment instrument that has been tested for validity and reliability. The COPE has been shown to be significantly correlated with corresponding scales of the Profile of Mood States and the Beck Depression Inventory and have a high test-retest reliability from cycle to cycle. While some studies have employed a battery of various psychometric tests (5), this instrument has been effective in differentiating PMDD patients from controls (27) and assessing improvement in response to treatment (7). The COPE asks subjects to self rate 22 symptoms grouped into behavioral (angry outbursts, crying easily, forgetfulness etc.) and physical (acne, breast tenderness etc) categories. Symptoms are rated daily on a 0 (none) to 3 (severe) scale.

Once this initial screening period was completed subjects were assessed for entry into the treatment phase of the study. Subjects with a documented overall COPE score 30% greater during the last seven days of the cycle (late luteal phase) compared to the first seven days of the cycle (NIMH Criteria)(28) were allowed to continue. Additionally, a thyroid panel, general serum chemistries, serum beta-human chorionic gonadotropin level, and a complete blood count were

performed at this phase. Any diagnosis of active disease that required further evaluation or treatment (hypothyroidism, hepatitis, pregnancy for example) resulted in exclusion from the study.

The 17 remaining subjects were randomly assigned to receive either Sertraline or placebo in the first treatment phase. Of these subjects, 11 completed the protocol over the seven cycle study period. Three women dropped out secondary to medication side effects (one of these was actually taking placebo), one moved away, and two discontinued for undetermined reasons. The initial treatment group received a daily dose of Sertraline 50 mg or placebo, from day 15 to the initial day of menses for two cycles. All subjects then underwent a washout cycle. Finally, the two groups were crossed over for the final two cycles of the study. Subjects completed the COPE calendar daily during the entire study period.

Subjects were seen by a physician investigator at regular monthly intervals throughout the initial and treatment phases of the study. These brief visits were structured to include assessment of side effects (a preprinted form with the most common side effects was administered), collection of COPE calendars, and performance of a serial serum pregnancy test during each of the treatment cycles. No psychotherapy was performed at these visits. The physicians were not aware of which treatment was being received by the patients.

For each reporting day, responses for the 22 symptoms on the COPE (each response measured on a four-point Likert scale of 0-3) were subdivided into a score for eight physical symptoms and a score for fourteen behavioral symptoms. Total scores for the late luteal phase (last seven days of the menstrual cycle) and for the initial follicular phase (first seven days of cycle) were then calculated. Baseline COPE scores for the luteal and follicular phases were compared using the paired t-test. For each phase, study periods (e.g., baseline, treatment month 1, washout, treatment month 2) were examined using repeated measures analysis of variance, with the within-subject factor, time period, and the between-subject factor, study drug order. To satisfy

assumptions of normality and homogeneity of variance for the model, scores were logarithmically transformed. Data was analyzed using SPSS 5.0 for Windows (SPSS Inc., Chicago, IL).

Based on previous placebo-controlled studies of treatment of PMDD with Fluoxetine and controlling the probability of a Type I error at alpha = 0.05, a sample of nine subjects was expected to have at least 80% power to detect a 70% difference in efficacy (90% fluoxetine vs. 20% on placebo) (21).

Results:

The mean age of the 11 women who completed the study was 36.9 years (range 23-43 years). Four subjects received placebo in the first treatment cycles and seven subjects received Sertraline initially. COPE score results for each study period are presented in Table 1.

Baseline behavioral COPE scores in the luteal phase were significantly higher compared to scores in the follicular phase (P=0.021), and there was a similar trend for physical symptoms (P=0.060). In the follicular phase, there was no significant difference in COPE scores between any of the four study periods (P=0.57 for behavioral symptoms and P=0.45 for physical symptoms) and study drug order was not a significant factor affecting COPE scores in this phase (P=0.23 for behavioral symptoms and P=0,16 for physical symptoms).

In the luteal phase, there was a significant difference between the four study periods (P=0.003 for behavioral symptoms and P=0.022 for physical symptoms). There was no significant difference between baseline and washout cycles (P=0.50 for behavioral symptoms and P=0.62 for physical symptoms) and the order in which the subject received the treatment did not significantly affect COPE scores in these untreated cycles (P=0.65 for behavioral symptoms and P=0.94 for physical symptoms).

When comparing COPE results during the treatment periods of the luteal phase, there was significant treatment effect, with higher COPE scores during the placebo cycles compared to the Sertraline treated cycles (P=0.0052 for

treatment periods of the luteal phase, there was significant treatment effect, with higher COPE scores during the placebo cycles compared to the Sertraline treated cycles (P=0.0052 for behavioral symptoms and P=0.012 for physical symptoms). The order in which the treatments were administered was not statistically significant (P=0.27 for behavioral symptoms and P=0,62 for physical symptoms). Behavioral COPE scores tended to decline from baseline during treatment with placebo (P=0.058, paired t-test), but the drop in physical scores during the placebo period was not statistically significant (P=0.45, paired t-test). During treatment with placebo, 8 women (73%) showed improvement from baseline in behavioral symptoms and 7 (64%) had lower physical COPE scores. When treated with Sertraline, 10 women (91%) had lower behavioral COPE scores compared to both the baseline and placebo periods, and 10 (91%) subjects had improved physical scores.

Discussion:

The efficacy of SSRIs in PMDD has been established in a number of previously cited studies. This is the first study that we know of that has treated PMDD patients solely during the luteal phase. We feel this approach raises important ideas from both etiologic and clinical perspectives.

Etiologic theories have focused on the similarities of PMDD to other psychiatric syndromes to include affective disorders, anxiety disorders, and opiate withdrawal. This latter theory stems from the fact that there appears to be a link between beta-endorphins and gonadal steroids (14,29),

b-endorphin neuronal cell bodies are concentrated in the arcuate nucleus where Gonadotropin Releasing Hormone (GnRH) and dopamine are also found (29), and that PMDD symptoms bear a number of similarities to opiate withdrawal. Studies of endorphin activity in PMDD patients have

tended to demonstrate a potential abnormality (30-32), though these findings are preliminary in nature and have not been consistently replicated (33). This model of a possible disruption in receptor activity due to an acute change in gonadal steroid levels was of particular interest to us, given the acute onset of PMDD symptoms, suggesting an etiology different from the much more gradually occurring affective disorders. Our observation of the effectiveness of an SSRI during only the luteal phase supports this idea of an acute change which can also be reversed on an acute basis. It is possible that an acute increase in serotonergic tone at least partially offsets changes in endogenous opiate binding caused by the rapid decrease in gonadal steroids typical of the luteal phase.

It is highly likely that symptom expression in PMDD involves a number of different steps at a central as well as peripheral level. The linking of ovarian hormones to neurotransmitter function (29), as well as clinical effects of prostaglandin inhibitors (mefenamic acid) (15) points to what is likely a chain of events that can be effected by manipulating various links.

Given the decline in behavioral COPE scores during the placebo period, this study reaffirms that placebo controlled trials are required to evaluate prospective treatments for this condition. Although the order in which treatment was received did not produce a statistically significant difference in the COPE scores, the lack of significance may be due to the small number of subjects in each sequence. Subjects were queried at the end of this study to test for the blinding of the treatment order, and all were able to correctly identify which treatment was received in each period.

Recent studies have shown some evidence of serotonin abnormalities in patients with PMDD (34), including significantly lowered whole blood serotonin as compared with controls during the last ten days of the menstrual cycle (13) and exacerbation of symptoms with tryptophan depletion (35). However, Fluoxetine may not be the best agent to increase serotonergic tone in this population. Sertraline is also an effective SSRI, but has a half life of approximately 24 hours,

compared to seven days for fluoxetine (and the active metabolite norfluoxetine), is more specific than fluoxetine, and of the available SSRIs in this country, has the least effect on the P450 IID6 system (36-7).

The potential advantages of Sertraline in PMDD include a much shorter washout period if the drug needs to be discontinued (this may be of particular importance in women considering pregnancy) and less drug-drug interaction due to Sertraline's higher specificity and minimal effect on hepatic enzymes. While the use of SSRI agents solely during the luteal phase needs further investigation, the practice may be important in terms of medication costs for the patient. In addition, this approach may be more attractive to patients and physicians dealing with the possibility of daily medication use for a large portion of a woman's reproductive years.

This trial provides strong evidence that use of Sertraline during the luteal phase is a viable treatment for PMDD.

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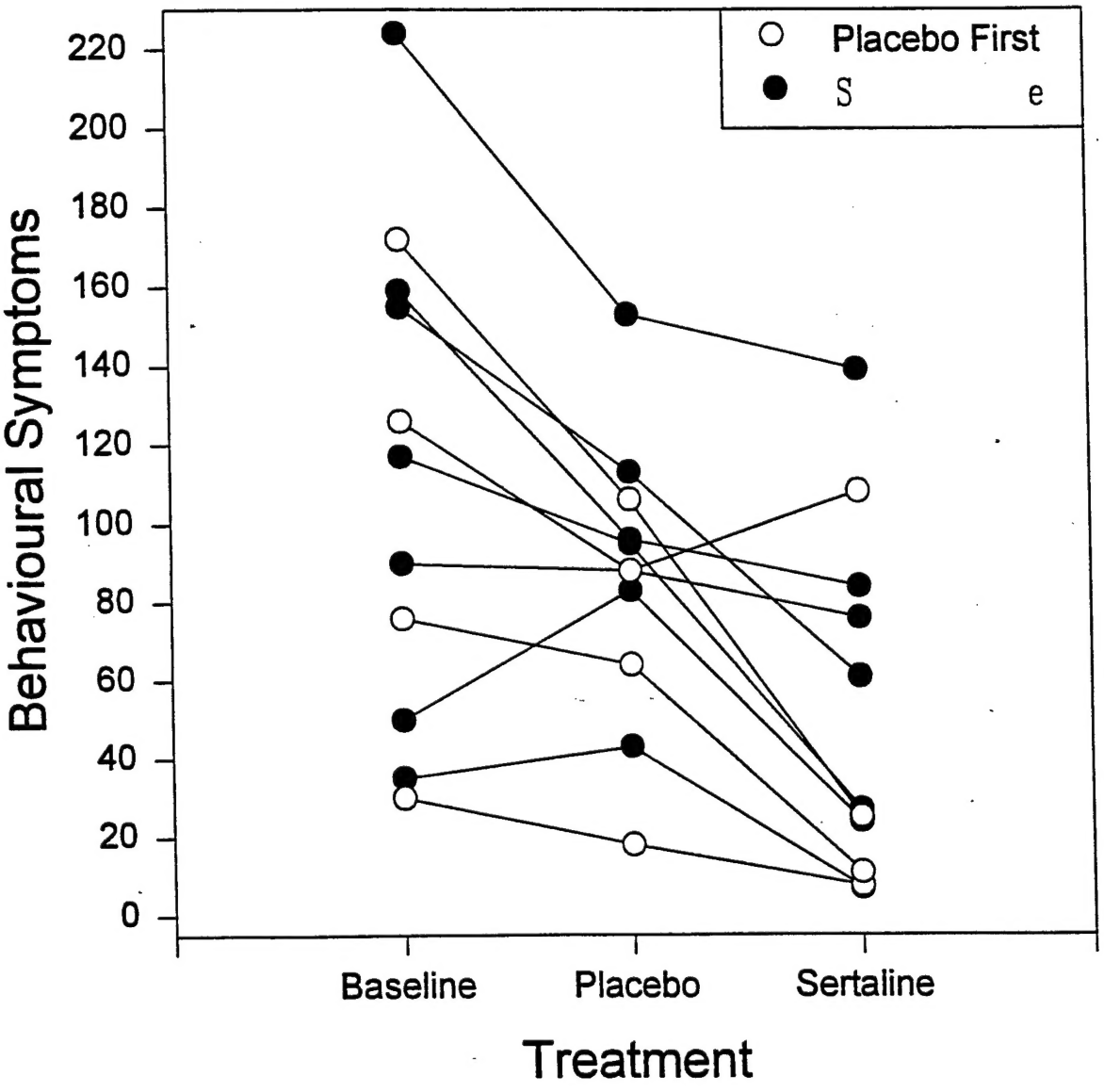
Placebo First
S e
Behavioural Symptoms
220
200
180
160
140
120
100
80
60
40
20
0
Baseline
Placebo
Sertaline
Treatment

Table 1

Study Period	Behavioral Cope Scores *Median (range)*		Physical Cope Scores *Median (range)*	
	Luteal	**Follicular**	**Luteal**	**Follicular**
Baseline	128 (36-286)	27 (0-199)	42 (11-162)	26 (0-133)
Washout	103 (34-273)	25 (0-115)	45 (15-158)	30 (0-168)
Placebo	88 (18-153)	62 (0-192)	45 (7-98)	30 (0-114)
Sertraline	27 (7-139)	31 (1-228)	24 (1-84)	19 (0-136)